



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2006

Parasagittal Asymmetries of the Corpus Callosum

Luders, E ; Narr, K L ; Zaidel, E ; Thompson, P M ; Jäncke, Lutz ; Toga, A W

Abstract: Significant relationships have been reported between midsagittal areas of the corpus callosum and the degree of interhemispheric transfer, functional lateralization and structural brain asymmetries. No study, however, has examined whether parasagittal callosal asymmetries (i.e. those close to the midline of the brain), which may be of specific functional consequence, are present in the human brain. Thus, we applied magnetic resonance imaging and novel computational surface-based methods to encode hemispheric differences in callosal thickness at a very high resolution. Discrete callosal areas were also compared between the hemispheres. Furthermore, acknowledging the frequently reported sex differences in callosal morphology, parasagittal callosal asymmetries were examined within each gender. Results showed significant rightward asymmetries of callosal thickness predominantly in the anterior body and anterior third of the callosum, suggesting a more diffuse functional organization of callosal projections in the right hemisphere. Asymmetries were increased in men, supporting the assumption of a sexually dimorphic organization of male and female brains that involves hemispheric relations and is reflected in the organization and distribution of callosal fibers

DOI: <https://doi.org/10.1093/cercor/bhi112>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-155030>

Journal Article

Published Version

Originally published at:

Luders, E; Narr, K L; Zaidel, E; Thompson, P M; Jäncke, Lutz; Toga, A W (2006). Parasagittal Asymmetries of the Corpus Callosum. *Cerebral Cortex*, 16(3):346-354.

DOI: <https://doi.org/10.1093/cercor/bhi112>

Parasagittal Asymmetries of the Corpus Callosum

E. Luders¹, K.L. Narr¹, E. Zaidel², P.M. Thompson¹,
L. Jancke³ and A.W. Toga¹

¹Laboratory of Neuro Imaging, Department of Neurology, Brain Mapping Division, UCLA School of Medicine, Los Angeles, USA, ²Department of Psychology, UCLA, Los Angeles, USA and ³Department of Neuropsychology, University of Zurich, Switzerland

Significant relationships have been reported between midsagittal areas of the corpus callosum and the degree of interhemispheric transfer, functional lateralization and structural brain asymmetries. No study, however, has examined whether parasagittal callosal asymmetries (i.e. those close to the midline of the brain), which may be of specific functional consequence, are present in the human brain. Thus, we applied magnetic resonance imaging and novel computational surface-based methods to encode hemispheric differences in callosal thickness at a very high resolution. Discrete callosal areas were also compared between the hemispheres. Furthermore, acknowledging the frequently reported sex differences in callosal morphology, parasagittal callosal asymmetries were examined within each gender. Results showed significant rightward asymmetries of callosal thickness predominantly in the anterior body and anterior third of the callosum, suggesting a more diffuse functional organization of callosal projections in the right hemisphere. Asymmetries were increased in men, supporting the assumption of a sexually dimorphic organization of male and female brains that involves hemispheric relations and is reflected in the organization and distribution of callosal fibers.

Keywords: gender, lateralization, hemispheres, morphology, sex

Introduction

The corpus callosum (CC) is the largest fiber tract in the human brain, connecting the two hemispheres through more than 200 million fibers (Aboitiz *et al.*, 1992b). Previous examinations of callosal size, shape and orientation on a macroscopic level have been complemented by insights from microscopic analyses, indicating that callosal connections are organized according to a number of specific rules. For example, as discussed in Clarke (2003a), each area of the cortex is connected with the corresponding area (homotopic callosal connections), as well as with non-corresponding regions (heterotopic callosal connections) in the contralateral hemisphere. Callosal connections are unevenly distributed across the cortical areas, although fibers connecting anterior brain regions travel primarily through the rostral CC, whereas fibers connecting posterior regions travel through the caudal CC. This topographic organization of callosal fibers, as well as positive relationships between total or partial callosal size and small diameter fibers (Aboitiz *et al.*, 1992b), suggest that regional callosal size is functionally significant. Numerous studies have therefore examined midsagittal callosal areas in relation to gender and age, as well as neuropsychiatric and neurodevelopmental disorders (e.g. schizophrenia and Down's syndrome). In addition, previous analyses have revealed significant relationships between midsagittal callosal area measurements and the degree of functional lateralization and/or structural asymmetries of other brain

structures (Habib *et al.*, 1991; Witelson and Goldsmith, 1991; Aboitiz, 1992; Aboitiz *et al.*, 1992a,c; Clarke and Zaidel, 1994; Zaidel *et al.*, 1995; Dorion *et al.*, 2000; Luders *et al.*, 2003). Remarkably, however, no study to date has yet addressed whether parasagittal callosal asymmetries exist at the anatomical level. Hemispheric asymmetries of callosal areas and/or callosal radiations measured parasagittally (i.e. close to the hemispheric midline) might evolve in association with functional specialization of the hemispheres and their associated cortical representations. For example, if homologous cortical regions have different morphological characteristics or locations in the left hemisphere (LH) and right hemisphere (RH), callosal fibers connecting these cortical regions may show different distributions depending on the region and hemisphere in which they are measured. Likewise, heterotopic callosal projections from the LH to the RH may be differently organized than those projecting from right to left. Indeed, there is both behavioral and physiological evidence for more efficient callosal motor transfer from the RH to the LH than vice versa (Braun *et al.*, 2003; Saron *et al.*, 2003; Zaidel and Iacoboni, 2003b,c). Altered fiber distributions (e.g. more spatially diffuse axons in one hemisphere compared to the other) as well as the organizational pattern of callosal projections might contribute to differences in callosal size between the hemispheres.

The main goal of the present study was to establish the presence and direction of parasagittal callosal asymmetries. That is, we examined hemispheric differences in callosal areas and thickness, as opposed to merely comparing the magnitude of callosal connections in different sections of the CC by analyzing midsagittal callosal areas. Differences between callosal areas and thickness were measured in the LH and RH several millimeters apart from the midsagittal plane. In order to achieve regionally specific measurements of the CC (in contrast to evaluating the CC as a whole), previous studies have applied several parcellation schemes. A widely used method to subdivide the midsagittal section of the CC into macroscopic subregions is the partition method proposed by Witelson (1989) and Clarke and Zaidel (1994). In these studies, the CC is arbitrarily divided into several regions according to maximal length, e.g. thirds: the anterior third containing primarily fibers that connect the prefrontal cortices, the mid-third (anterior and posterior body) primarily connecting the motor, somatosensory and auditory cortices, and the posterior third (isthmus and splenium) predominantly connecting temporal, parietal and occipital areas. Others have used a different approach by subjecting midsagittal callosal width measurements, made along the longitudinal axis, to factor analysis techniques that have generated six or seven regional clusters on average (Kertesz *et al.*, 1987; Denenberg *et al.*, 1989, 1991; Allen *et al.*, 1991;

Cowell *et al.*, 1994; Peters *et al.*, 2002). However, parcellation schemes based on geometrical solutions (e.g., the Witelson scheme) could be biased by local variability in callosal shape, while measures based on statistically defined internal cohesiveness (factor analysis) could produce factors that do not necessarily correspond to any functional boundaries. To circumvent these issues, we developed a novel computational strategy to isolate highly localized differences in callosal thickness between the hemispheres. This method does not rely on parcellating the CC. Instead, anatomical surface mesh modeling methods are employed to encode hemispheric differences in the regional thickness of the CC at subvoxel resolution. In order to assess the validity and statistical power of our novel thickness-mapping approach, we also analyzed parasagittal callosal asymmetries based on the traditional geometrical parcellation scheme described above.

Finally, gender differences in callosal morphology measures have been reported frequently (for a review see Bishop and Wahlsten, 1997), although not always replicated, and gender differences have been demonstrated in the relationship between callosal size or fiber numbers and structural asymmetry or functional lateralization (Witelson and Goldsmith, 1991; Aboitiz, 1992; Aboitiz *et al.*, 1992a,c; Clarke and Zaidel, 1994; Zaidel *et al.*, 1995; Dorion *et al.*, 2000; Luders *et al.*, 2003). Therefore, we also examined parasagittal callosal asymmetries in men and women separately.

Materials and Methods

Subjects

We analyzed the brains of 60 right-handed healthy subjects selected from a database of high-resolution anatomical MR images acquired at the Center for Neuroscientific Innovation and Technology (ZENIT), Magdeburg. Male and female subjects were matched in terms of numbers (30 women, 30 men) and age (women: 24.32 ± 4.35 years; men: 25.45 ± 4.72 years). Young adults with a relatively narrow age range were recruited so as to minimize the influences of age and possible interactions of age with gender, which have been demonstrated to influence the number of callosal fibers present (Aboitiz *et al.*, 1996). Handedness was determined by referring to self-reports of hand preference. Subjects were volunteers and included university students from different fields who were recruited via notice board and/or Internet advertisements. All subjects gave informed consent according to institutional guidelines (Ethics Committee of the University of Magdeburg).

MRI Acquisition

Images were obtained on a 1.5-T MRI system (General Electric, Waukesha, WI, USA) using a T1-weighted spoiled gradient echo pulse sequence with the following parameters: $T_R = 24$ ms, $T_E = 8$ ms, 30° flip angle, FOV = 250×250 mm², matrix size = $256 \times 256 \times 124$, voxel size = $0.98 \times 0.98 \times 1.5$ mm.

Image Preprocessing

First, image volumes were placed into the standard coordinate system of the ICBM-305 average brain using a three-translation and three-rotation rigid-body transformation (Woods *et al.*, 1998). This procedure corrects for differences in head alignment between subjects to assure that asymmetry measurements are not influenced by different brain orientations. One rater, blind to gender, delineated the CC 6 mm from the midsagittal sections (parasagittal) in the LH and RH (Fig. 1). If it was not possible to clearly discriminate the CC at 6 mm from midline, the CC was outlined at 5 or 4 mm from the midsagittal section in both hemispheres. Midsagittal brain sections were defined by identifying the interhemispheric fissure in the coronal and sagittal planes and confirmed by the presence of the falx cerebri. In order to be able to relate parasagittal area measures to a baseline, we also delineated the

CC directly in the midsagittal sections, as done in classical CC studies (Fig. 1). For inter-rater reliability, two independent investigators (E.L. and K.N.) contoured the CC from six different randomly selected brains. The intraclass correlation coefficient obtained for total CC size area was $r = 0.99$.

Area Measurements

In accordance with the traditional approach of performing regional analyses, the callosal renderings from each hemisphere as well as from the midline were reoriented to maximize callosal length and divided into five vertical partitions representing (1) the splenium, (2) the isthmus, (3) the posterior midbody, (4) the anterior midbody and (5) the anterior third as visualized in Figure 1 (Witelson, 1989). Of note, these callosal outlines were established on images that were corrected for brain alignment but not for brain size. Therefore, callosal area measures that were acquired in mm² for each callosal segment are uncorrected for individual brain volumes and are hereafter referred to as unscaled measures. Paired *t*-tests were applied to compare unscaled callosal area measurements between the LH and RH for the whole sample, with a Bonferroni correction applied for the five separate comparisons. Thus, a corrected alpha level of $P \leq 0.01$ was employed as the new criterion for significance. If a comparison revealed a significant difference between left and right callosal measures, follow-up analyses were conducted to examine hemispheric differences in callosal size within males and females separately. In addition, asymmetry coefficients for unscaled callosal area measurements were calculated using the formula $(\text{left} - \text{right}) / 0.5(\text{left} + \text{right})$. Given that magnitudes of left-right differences are greater in larger brains, these relative measures between hemispheres are useful to examine parasagittal callosal asymmetries that are mediated independently of differences in brain size. One-sample *t*-tests were applied to asymmetry coefficients to examine parasagittal callosal asymmetries, with Bonferroni corrections and follow up tests concerning effects within each gender conducted as described above.

Surface-based Thickness Measurements

To obtain highly localized measures of callosal thickness for across-hemisphere comparisons, anatomical surface based mesh modeling methods were employed. Callosal thickness mapping was performed after correcting brains for head position and tilt but preserving original brain sizes (hereafter referred to as *unscaled data*). That is, 6-parameter transformations were used to reorient the data and to place it into the co-ordinate space of the ICBM-305 average brain created by the International Consortium for Brain Mapping (Mazziotta *et al.*, 1995). However, based on the assumption that individual brain sizes might influence the magnitude of parasagittal callosal asymmetries, callosal thickness mapping was further applied to callosal outlines after correcting for individual differences in brain size using 12-parameter transformations to convert the data into the dimensions of the ICBM-305 average brain (hereafter referred to as *scaled data*). Scaled and unscaled callosal outlines from the LH and RH were automatically divided into top and bottom segments as illustrated in Figure 2. The randomly digitized points making up each callosal surface were then redigitized to render them spatially uniform using surface-based mesh modeling methods (Thompson *et al.*, 1996a,b, 1997). Subsequently, the 2D average (the medial CC line) was calculated from spatially homologous surface points representing the upper (top) and lower (bottom) callosal surface boundaries in each hemisphere. Finally, the distances between each of 100 equidistant surface points making up the medial CC line and 100 equidistant surface points making up the callosal surface boundaries (top and bottom) were calculated for the LH and RH (Fig. 2). This system using 100 points is somewhat comparable to Denenberg's approach dividing the midsagittal CC area into 99 percentile widths along a curved longitudinal axis (Denenberg *et al.*, 1991). However, in contrast to subjecting these width measures to factor analysis in order to reveal regional clusters as Denenberg did, our approach provides us with pointwise distance measures at each of the 100 surface points estimating the local thickness of the CC. Hemispheric differences in callosal thickness measures were assessed by applying paired *t*-tests at each of the 100 callosal surface points for the whole sample and for males and females separately. Regions exhibiting significant differences were coded in color and mapped onto the

Callosal Measurements

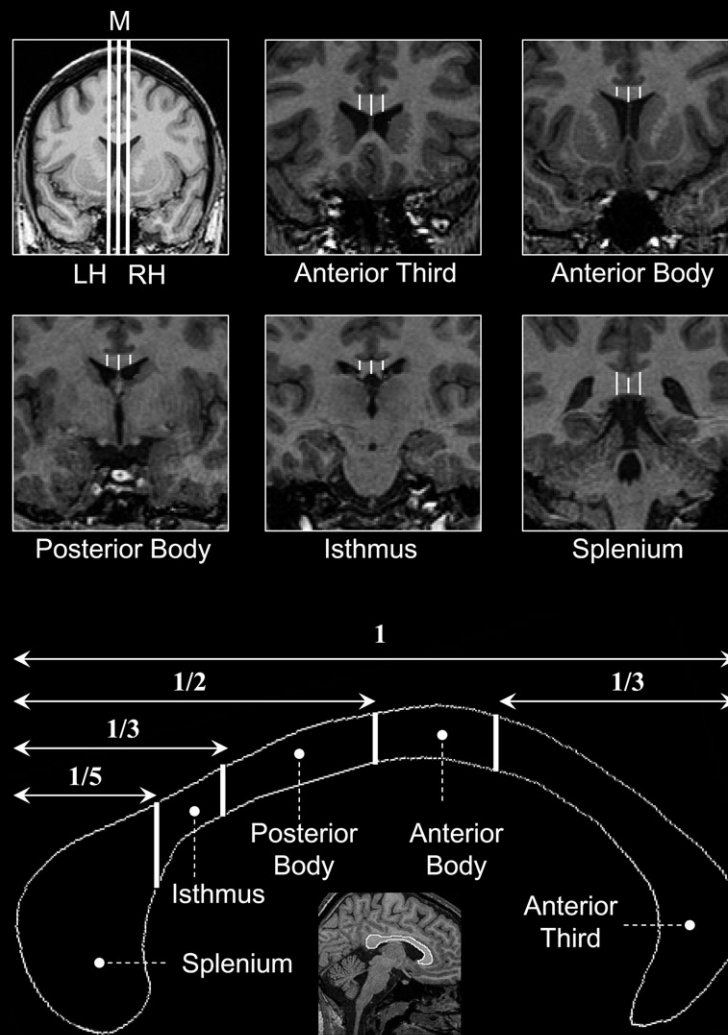


Figure 1. Illustration of callosal outlining and area measurements. Top panel: the CC was delineated in midsagittal brain sections (M) as well as in the left (LH) and right (RH) hemisphere 6 mm off midline (indicated by the three white lines in the coronal view). Descriptively, midsagittal callosal sections in the anterior third, anterior body, posterior body and isthmus (but not splenium) appear to be thicker than parasagittal sections, as demonstrated on a random brain from the sample. Bottom panel: the partitioning scheme adapted from Witelson (1989) and Clarke and Zaidel (1994) was employed to divide the CC perpendicular to its maximal length, into the splenium (representing the posterior fifth of callosal area), the isthmus (representing two fifteenths), the posterior midbody and anterior midbody (each representing one sixth), and the anterior third (as shown).

average callosal surface model. In addition, we generated color-coded variability maps to provide detailed information about the variance of parasagittal thickness measures. For this purpose, we calculated the SD of callosal thickness measures from equivalent surface points in each individual in groups defined by gender (males, females, all subjects), scaling (scaled, unscaled) and callosal segment (top, bottom).

Results

Callosal Area Measurements and Asymmetry

Table 1 shows means and SDs for callosal area measures obtained for the overall sample and for males and females separately. Midsagittal areas are larger than parasagittal areas for the callosal anterior third, anterior body, posterior body and

isthmus. Only the splenium appears to have a larger area in the LH and RH compared to the midline. The comparison of left and right callosal measurements revealed significantly larger areas in the right anterior body [$t(1,59) = 2.9$, $P \leq 0.007$] compared to the left. Follow-up tests confirmed larger right-hemispheric anterior bodies in males [$t(1,59) = 2.7$, $P \leq 0.014$] which were below the threshold of significance in females [$t(1,59) = 1.2$, $P \leq 0.232$].

Similarly, the one-sample t -tests applied to the callosal asymmetry coefficients revealed a significant rightward asymmetry for the anterior body within the entire study group [$t(1,59) = 2.8$, $P \leq 0.006$] and in males [$t(1,59) = 2.4$, $P \leq 0.023$], but not in females [$t(1,59) = 1.5$, $P \leq 0.133$]. None of the other comparisons resulted in statistically significant results.

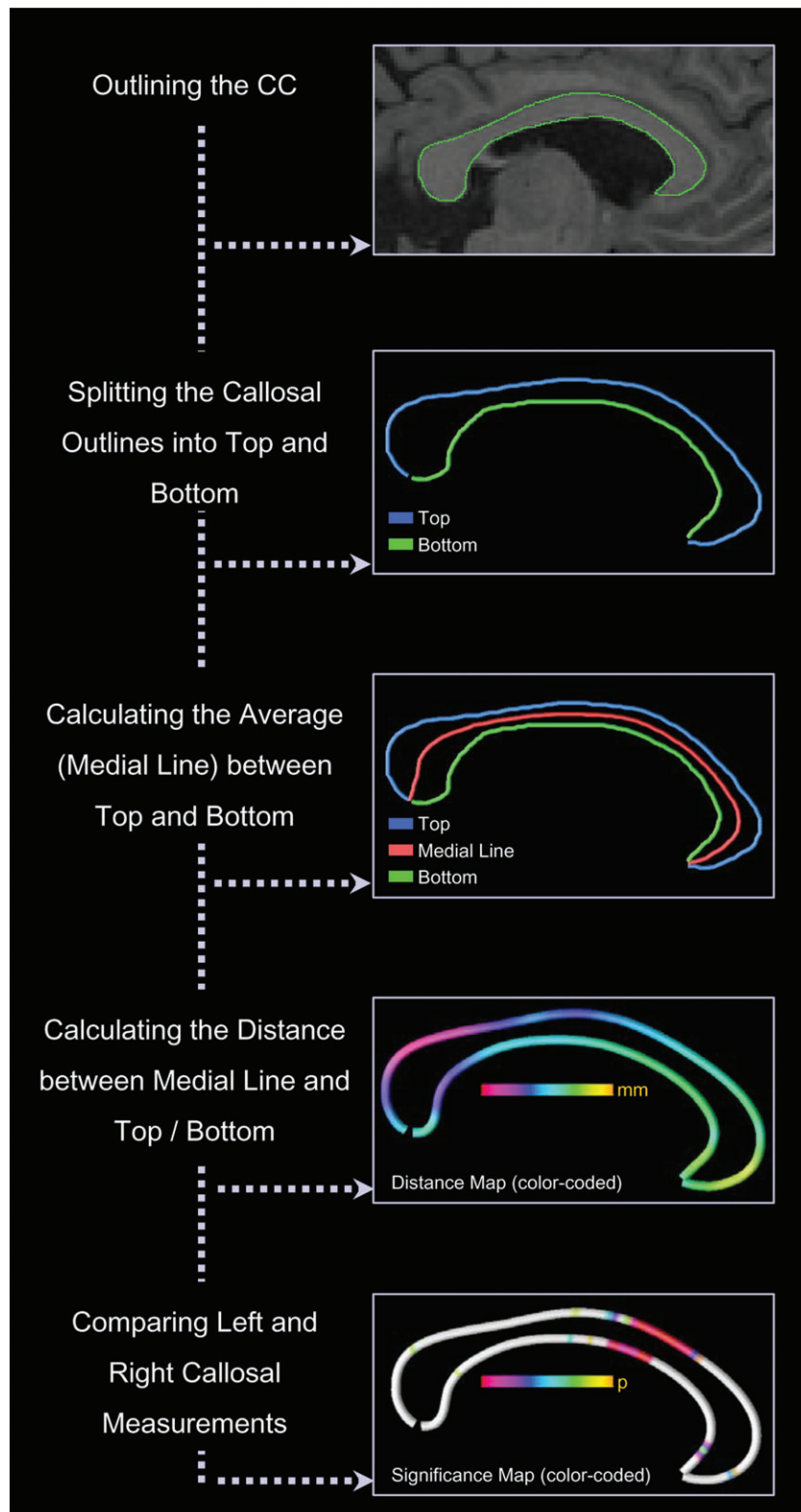


Figure 2. Illustration of callosal thickness measurements. After tracing the CC in the LH and RH, the callosal outlines were split into superior (top) and inferior surfaces (bottom); subsequently a medial line was created equidistant to these surfaces. The distances between the medial line and the superior and inferior surfaces were calculated for left and right callosal measurements. Finally, hemispheric differences in callosal thickness were assessed by applying paired *t*-tests within the whole sample and for males and females separately. Regions exhibiting significant differences were coded in color and mapped onto the average callosal surface model.

Table 1Means and SDs of unscaled area measures in mm² (uncorrected for individual brain volumes)

	Total <i>n</i>		Males		Females	
	Right	Left	Right	Left	Right	Left
Parasagittal measures						
Anterior third	235.9 (40.2)	234.2 (38.7)	248.2 (45.9)	243.0 (43.8)	223.7 (29.6)	225.3 (31.2)
Anterior midbody ^a	63.1 (11.3)	60.5 (10.0)	66.7 (13.6)	62.8 (10.3)	59.5 (6.9)	58.2 (9.3)
Posterior midbody	55.7 (9.6)	54.8 (9.0)	56.7 (11.2)	57.0 (10.2)	54.7 (7.9)	52.6 (6.9)
Isthmus	44.0 (10.4)	44.3 (10.6)	45.8 (11.0)	47.2 (11.8)	42.2 (9.7)	41.4 (8.4)
Splenium	176.8 (34.6)	177.1 (34.0)	185.6 (41.9)	186.8 (41.3)	167.9 (22.8)	167.4 (21.2)
Midsagittal measures						
Anterior third	248.0 (36.4)		257.4 (39.7)		238.5 (30.6)	
Anterior midbody	73.9 (11.2)		76.9 (11.9)		70.9 (9.9)	
Posterior midbody	66.1 (10.0)		67.7 (11.4)		64.5 (8.3)	
Isthmus	54.3 (12.6)		57.1 (13.3)		51.4 (11.3)	
Splenium	172.2 (33.2)		180.7 (38.7)		163.7 (24.4)	

^aA significant rightward asymmetry was detected within the whole study group and in males using paired *t*-tests.

Asymmetry coefficients for each callosal segment are presented in Table 2.

Callosal Thickness Asymmetry

Hemispheric differences in callosal thickness measurements, both uncorrected (unscaled) and corrected (scaled) for individual brain volumes, are illustrated as color-coded significance maps in Figure 3. The color bar encodes the *P*-value, with white color indicating regions where no significant asymmetries were detected. Unscaled callosal measurements in the whole sample revealed significant rightward asymmetries in regions corresponding to the anterior body and anterior third (defined according to the classical parcellation scheme). Rightward asymmetry in those regions means that the pointwise distance measures from midline to upper (top) and/or lower (bottom) callosal surface boundaries were larger in the RH than the LH. While rightward asymmetries are situated exclusively at the beginning and end of the callosal anterior third, almost the entire callosal anterior body demonstrates a rightward asymmetry. Males showed rightward asymmetries in similar locations, while rightward asymmetry in females seems to be reduced to smaller callosal regions with diminished significance in the anterior body, in the anterior third and at the border between the isthmus and splenium (Fig. 3, left). Rightward asymmetries of scaled callosal measurements are situated in comparable regions as revealed in the unscaled data (anterior body/anterior third, isthmus/splenium), where asymmetric regions seem to be more diffuse and widespread in the anterior body (Fig. 3, right). In contrast, there was no callosal region demonstrating significant leftward asymmetries in unscaled callosal data, and only minor regions of marginal leftward asymmetry in the isthmus (males) and splenium (whole group, females) when brain size corrections were applied.

Callosal Thickness Variability

The distributional pattern of callosal thickness variability in parasagittal sections, shown in Figure 4, appears to be similar between the two hemispheres and between males and females, although slightly lower values were observed in the LH and in females. In callosal subregions, higher variabilities are seen in all groups (defined by gender, hemisphere and scaling) somewhat superior to the most bulbous parts of the callosal anterior thirds and the splenium (partly extending into the isthmus). In con-

Table 2

Means and SDs of asymmetry coefficients for unscaled callosal area measures (uncorrected for individual brain volumes)

	Total <i>n</i>	Males	Females
Anterior third	−0.007 (0.078)	−0.021 (0.083)	0.006 (0.072)
Anterior midbody ^a	−0.040 (0.109)	−0.052 (0.118)	−0.028 (0.099)
Posterior midbody	−0.014 (0.127)	0.010 (0.117)	−0.038 (0.134)
Isthmus	0.007 (0.149)	0.027 (0.141)	−0.013 (0.155)
Splenium	0.003 (0.058)	0.008 (0.056)	−0.001 (0.060)

Positive values indicate leftward asymmetry, negative values indicate rightward asymmetry.

^aA significant rightward asymmetry was detected within the whole study group and in males using one-sample *t*-tests.

trast, lower callosal variabilities were detected in LH and RH regions corresponding to the anterior and posterior body, and at the very tip of the anterior third and splenium.

Discussion

In the present study we compared callosal measurements from the LH and RH by applying novel computational surface-based methods to encode hemispheric differences in callosal thickness. The advantage of the new thickness approach is that callosal peculiarities (e.g. thickness) and its statistical descriptors (e.g. variability) can be isolated at a subvoxel resolution without relying on parcellation schemes (that could be biased by local variability in callosal shape) or other measures based on statistically defined internal cohesiveness (that could produce factors that do not necessarily correspond to any functional boundaries). Furthermore, rather than just presenting area measurements, our novel thickness approach allows us to visualize callosal morphology and group-specific properties through color-coded shape profiles.

In the present study we detected significant rightward asymmetries of callosal size and thickness, predominantly in regions corresponding to the anterior body of the CC. Although many previous investigations have revealed functional and structural hemispheric asymmetries and have demonstrated associations between callosal size and cortical asymmetries, to our knowledge, parasagittal callosal asymmetry itself has not been addressed empirically, and thus comparable data do not exist. Notwithstanding this, in the present study we conducted supplementary measurements of midsagittal areas (like in classic

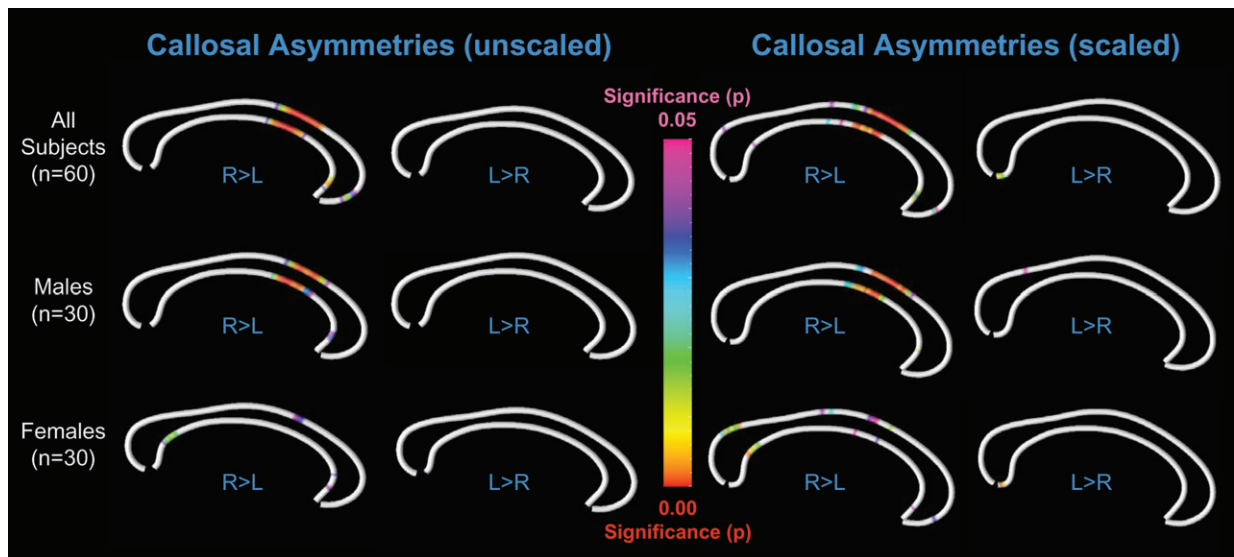


Figure 3. Callosal asymmetries in unscaled data after using six parameter transformations to correct for head alignment only (left) and in scaled data after using 12 parameter transformations to correct for brain size (right). Rightward ($R > L$) and leftward asymmetries ($L > R$) are depicted for the whole sample, and in males and females separately. The callosal anterior third is located on the right and the splenium on the left. The color bar encodes the P -value, with white color indicating regions where no significant asymmetries were detected.

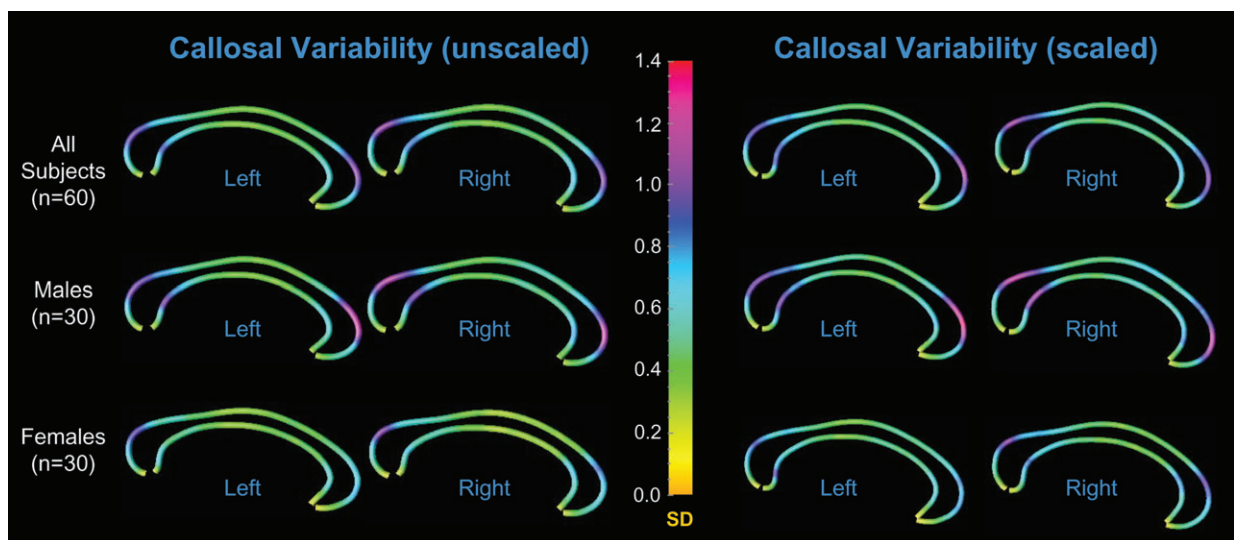


Figure 4. Callosal thickness variability mapped for the whole group in unscaled data after using six parameter transformations (left) and in scaled data after using 12 parameter transformations (right). The color bar encodes the SD of callosal thickness measures from equivalent surface points in each individual in groups defined by gender (males, females, all subjects), scaling (scaled, unscaled) and callosal segment (top, bottom).

CC analyses) in order to have a baseline against which our parasagittal area measures could be compared. Interestingly, the absolute cross-section area of the CC was smaller parasagittally than midsagittally. This most likely reflects ‘physical constraints’ in the pathway of callosal fibers, given that the roof of the frontal horn of the lateral ventricles is slightly angled (Fig. 1). Consequently, smaller areas are measured in the LH and RH compared with the midline in the callosal section of the anterior third, anterior body, posterior third and isthmus. In contrast, larger parasagittal than midsagittal area measurements were observed for the splenium, likely due to the vanishing impact of the morphology of the lateral ventricle on parasagittal splenial sections (Fig. 1). It would be interesting for future studies to

chart the course of change in cross-section areas with distance from the midsagittal plane, and to investigate whether ‘mechanical constraints’ may mediate the evolution of parasagittal callosal asymmetry and with it the functional asymmetry of the cerebral cortex.

Regardless of the relationship between midsagittal and parasagittal area measures, our observations of rightward asymmetry are of great interest. Irrespective of the region, hemispheric asymmetries of callosal size could be the result of fiber radiations that are more spread out horizontally (anterior-posterior) and/or vertically (inferior-superior) in one hemisphere than in the other. However, although callosal area asymmetries may be attributable to changes in callosal length (horizontal dispersions),

this is not likely to be the predominant cause of the parasagittal callosal asymmetries observed in the present analysis. The main reason is that callosal area comparisons revealed very similar results to thickness comparisons, which are more sensitive to vertically than to horizontally altered dimensions. Furthermore, if hemispheric differences existed in the horizontal fiber dispersion, they would probably not appear as significant asymmetries exclusively in the anterior body (as shown in the area analysis), given that subdivisions were created according to maximal callosal length. Our results thus support the hypothesis that hemispheric asymmetries of callosal size (area and thickness measurements) are attributable to callosal radiations that are more diffusely organized in the vertical dimension in the RH than in the LH.

In agreement with our findings of rightward parasagittal callosal asymmetries, prior lesion data indicate that circumscribed damage to the LH may result in more focused functional deficits since fibers and function in the RH are more diffusely arranged (Tompkins, 1995; Zaidel *et al.*, 2000; Soroker *et al.*, 2005). Similarly, neurophysiological data suggests that RH functions are more diffusely represented in the cortex than corresponding functions in the LH (Semmes, 1968). The most significant and distinct parasagittal callosal asymmetry was detected in the anterior body — a callosal region that contains predominantly projections from the motor cortices (Aboitiz *et al.*, 1992a,b). Different expansions and/or locations of functionally homologous regions in the motor cortex might condition a regionally extended spatial distribution of homotopic callosal fibers in one hemisphere compared to the other, which may account for the observed parasagittal callosal asymmetry. Different anatomical characteristics of the motor cortices in the LH and RH might be indirectly related to hemisphere-specific functional specializations and behavioral asymmetries. For example, since we exclusively analyzed brains of right-handers, the detected asymmetry in the size of the callosal anterior body might be associated with the dominance of the LH for motor functions of the right hand. The literature suggests an increased area of hand representation in the motor cortex of the dominant hemisphere relative to the non-dominant hemisphere (Hammond, 2002). The size of the areas in the motor cortex devoted to controlling the different muscle groups is often unrelated to the physical dimensions of the body region activated by those muscle groups (Penfield and Boldrey, 1937). Given that muscles controlling the hand and finger are heavily represented, it is likely that asymmetric cortical representations of the hand in the motor cortex of the LH and RH accompany asymmetries in the cortical representation of other limb and face segments. Asymmetries in cortical representations beyond a certain magnitude might be associated with asymmetric fiber distributions, which, in turn, could be reflected in regional asymmetries of callosal size. Investigations at the cellular level indicate that the maintenance and elimination of axonal processes in the CC can be modified by changes in cortical structure. This lends further support to the hypothesis that the organization of callosal fibers might be closely linked to the size, internal organization and cellular composition of cortical areas (Innocenti, 1995). Our hypothesis that anatomical and functional asymmetries might be closely related to parasagittal callosal asymmetries complements classic theories predicting an inverse relationship between the degree of anatomical asymmetry and callosal size (Galaburda *et al.*,

1990). Our results might also possibly augment former hypotheses suggesting that greater structural/functional asymmetry is associated with a decrease in the size of the nondominant hemisphere, as well as with an increase of intrahemispheric connectivity (Galaburda *et al.*, 1990).

Cortical regions that are known to be asymmetrical may receive and give rise to numerous and widespread heterotopic callosal connections (Clarke, 2003a,b). That is, instead of hemispheric differences in the spatial distribution of homotopic callosal fibers, or in addition to these differences, parasagittal callosal asymmetries could be influenced by the organizational pattern of heterotopic callosal connections between non-corresponding regions. For example, a particular region in the LH might project to a whole set of contralateral (right-hemispheric) areas. In contrast, fibers originating from this particular region in the RH might project (i) only to the homologous area in the LH, (ii) to a smaller number of contralateral areas or (iii) to areas that are more restricted in their spatial distribution. As summarized by Innocenti and Bressoud (2003), although callosal connections are reciprocal and roughly symmetrical, non-symmetrical connections can be generated experimentally, and thus must be expected to exist in anatomically or functionally asymmetric brains.

Our gender-specific findings of parasagittal callosal asymmetry might lend further support to the hypothesis that regional inter-hemispheric connectivity is adjusted to local characteristics (e.g. structural asymmetry) of the cortex. More precisely, hemispheric differences of callosal thickness and area measurements were more pronounced and significant in males than in females, which might be related to the decreased anatomical asymmetry and functional lateralization often observed in females (Lake and Bryden, 1976; Kulynych *et al.*, 1994; Kansaku *et al.*, 2000; Good *et al.*, 2001; Hiscock *et al.*, 2001; Medland *et al.*, 2002). The present study revealed distinctive and extensive asymmetries in the anterior body and additionally in a small and less significant region in the anterior third of the CC of males. In contrast, asymmetry in females was less significant in general and applied to smaller callosal regions in the anterior body, in the anterior third and additionally at the border between the isthmus and splenium. Interestingly, the distinctive asymmetry in the anterior callosal body detected in the whole sample and in males disappeared when females were analyzed separately. Given that both men and women had slightly higher variance in the right hemisphere (Fig. 4), there seems to be no evidence that diminished asymmetries in female brains are a result of a gender-specific variance of callosal thickness in one hemisphere or the other. Our findings are of particular interest considering previous results which indicated that right-handed males show significantly different depths of the central sulcus in the two hemispheres, whereas no interhemispheric asymmetry was found in females (Amunts *et al.*, 2000). Similarly, functional imaging revealed sex differences in peri-rolandic asymmetries in a tactile discrimination task, where females predominantly activated both premotor cortices but males showed an asymmetric activation (Sadato *et al.*, 2000). Additionally, there seems to be a partial convergence between the female asymmetry of the CC at the isthmus-splenium border, observed here, and a negative correlation between Sylvian fissure asymmetry and cross-section size of the anterior splenium in females and the isthmus in males (Aboitiz, 1992; Aboitiz *et al.*, 1992a; Zaidel *et al.*, 1995). These observations might indicate

that left superior-posterior temporal language areas are more posteriorly organized in females than in males, and that they project to a larger posterior 'language-related' area in the RH. Taken together, prior findings and the results of the present study may suggest a dimorphic organization in the brains of men and women which seems to be reflected in the organization and distribution of callosal fibers.

Summary

The present analysis revealed hemispheric differences in callosal fiber distributions that may be associated with the structural asymmetries of particular cortical regions and associated functional lateralization. That is, cortical asymmetry and functional lateralization might not be related only to midsagittal callosal size, as suggested in previous studies, but also to parasagittal callosal asymmetry itself. The magnitude of hemispheric asymmetry in regional callosal size may be influenced by the degree of asymmetry between corresponding cortical regions connected through these callosal fibers. However, further studies are clearly necessary to systematically evaluate to what extent such relationships exist. In addition, future studies may explore whether parasagittal callosal asymmetry contributes to the generation of functional lateralization or whether structural asymmetry and functional hemispheric specialization may affect parasagittal callosal asymmetry. Notwithstanding, the present findings serve to generate hypotheses about the functional significance of parasagittal callosal asymmetry and to inspire further research dealing with the morphological substrate of interhemispheric interaction.

Notes

This work was funded by the National Institutes of Health through the NIH Roadmap for Medical Research (U54 RR021813). This work was also supported by research grants from the National Library of Medicine and National Institute on Aging (R01 LM05639), National Institute of Mental Health and National Institute of Neurological Disorders and Stroke (P20 MH065166, NS 20187), resource grants from the National Center for Research Resources (P41 RR013642 & M01 RR000865), an NIMH NRSA Training Grant (MH14584) and a Daniel X. Freedman NARSAD Young Investigator Award (to K.L.N.), and R21 grants RR19771 and EB01561 (to P.T.). Additional support was provided by the National Institute of Biomedical Imaging and Bioengineering, National Institute of Neurological Disorders and Stroke, and National Institute of Mental Health (P01 EB001955). We thank Karen Schrock for proofreading the manuscript.

Address correspondence to Dr Arthur W. Toga, Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine. 710 Westwood Plaza, 4238 Reed, Los Angeles, CA 90095-1769, USA. Email: toga@loni.ucla.edu.

References

Aboitiz F (1992) Brain connections: interhemispheric fiber systems and anatomical brain asymmetries in humans. *Biol Res* 25:51–61.
Aboitiz F, Scheibel AB, Fisher RS, Zaidel E (1992a) Individual differences in brain asymmetries and fiber composition in the human corpus callosum. *Brain Res* 598:154–161.
Aboitiz F, Scheibel AB, Fisher RS, Zaidel E (1992b) Fiber composition of the human corpus callosum. *Brain Res* 598:143–153.
Aboitiz F, Scheibel AB, Zaidel E (1992c) Morphometry of the Sylvian fissure and the corpus callosum, with emphasis on sex differences. *Brain* 115:1521–1541.

Aboitiz F, Rodriguez E, Olivares R, Zaidel E (1996) Age-related changes in fibre composition of the human corpus callosum: sex differences. *Neuroreport* 7:1761–1764.
Allen LS, Richey MF, Chai YM, Gorski RA (1991) Sex differences in the corpus callosum of the living human being. *J Neurosci* 11:933–942.
Amunts K, Jancke L, Mohlberg H, Steinmetz H, Zilles K (2000) Interhemispheric asymmetry of the human motor cortex related to handedness and gender. *Neuropsychologia* 38:304–312.
Bishop KM, Wahlsten D (1997) Sex differences in the human corpus callosum: myth or reality? *Neurosci Biobehav Rev* 21:581–601.
Braun CMJ, Achim A, Larocque C (2003) The evolution of the concept of interhemispheric relay time. In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 237–258. Cambridge, MA: MIT Press.
Clarke JM, Zaidel E (1994) Anatomical-behavioral relationships: corpus callosum morphometry and hemispheric specialization. *Behav Brain Res* 64:185–202.
Clarke S (2003a) Complexity of human interhemispheric connections. In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 47–49. Cambridge, MA: MIT Press.
Clarke S (2003b) The role of homotopic and heterotopic callosal connections in humans. In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 461–472. Cambridge, MA: MIT Press.
Cowell PE, Allen LS, Kertesz A, Zalaito NS, Denenberg VH (1994) Human corpus callosum: a stable mathematical model of regional neuroanatomy. *Brain Cogn* 25:52–66.
Denenberg VH, Berrebi AS, Fitch RH (1989) A factor analysis of the rat's corpus callosum. *Brain Res* 497:271–279.
Denenberg VH, Kertesz A, Cowell PE (1991) A factor analysis of the human's corpus callosum. *Brain Res* 548:126–132.
Dorion AA, Chantome M, Hasboun D, Zouaoui A, Marsault C, Capron C, Duyme M (2000) Hemispheric asymmetry and corpus callosum morphometry: a magnetic resonance imaging study. *Neurosci Res* 36:9–13.
Galaburda AM, Rosen GD, Sherman GF (1990) Individual variability in cortical organization: its relationship to brain laterality and implications to function. *Neuropsychologia* 28:529–546.
Gardner H, Brownell HH (1986) Right hemisphere communication battery. Boston, MA: Psychology Service, VAMC.
Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* 14:685–700.
Habib M, Gayraud D, Oliva A, Regis J, Salamon G, Khalil R (1991) Effects of handedness and sex on the morphology of the corpus callosum: a study with brain magnetic resonance imaging. *Brain Cogn* 16:41–61.
Hammond G (2002) Correlates of human handedness in primary motor cortex: a review and hypothesis. *Neurosci Biobehav Rev* 26:285–292.
Hiscock M, Perachio N, Inch R (2001) Is there a sex difference in human laterality? IV. An exhaustive survey of dual-task interference studies from six neuropsychology journals. *J Clin Exp Neuropsychol* 23:137–148.
Innocenti GM (1995) Exuberant development of connections, and its possible permissive role in cortical evolution. *Trends Neurosci* 18:397–402.
Innocenti GM, Bressoud R (2003) Callosal axons and their development. In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 11–26. Cambridge, MA: MIT Press.
Kansaku K, Yamaura A, Kitazawa S (2000) Sex differences in lateralization revealed in the posterior language areas. *Cereb Cortex* 10:866–872.
Kertesz A, Polk M, Howell J, Black SE (1987) Cerebral dominance, sex, and callosal size in MRI. *Neurology* 37:1385–1388.
Kulynych JJ, Vladar K, Jones DW, Weinberger DR (1994) Gender differences in the normal lateralization of the supratemporal cortex: MRI surface-rendering morphometry of Heschl's gyrus and the planum temporale. *Cereb Cortex* 4:107–118.
Lake DA, Bryden MP (1976) Handedness and sex differences in hemispheric asymmetry. *Brain Lang* 3:266–282.

- Luders E, Rex DE, Narr KL, Woods RP, Jancke L, Thompson PM, Mazziotta JC, Toga AW (2003) Relationships between sulcal asymmetries and corpus callosum size: gender and handedness effects. *Cereb Cortex* 13:1084-1093.
- Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J (1995) A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). *Neuroimage* 2:89-101.
- Medland SE, Geffen G, McFarland K (2002) Lateralization of speech production using verbal/manual dual tasks: meta-analysis of sex differences and practice effects. *Neuropsychologia* 40:1233-1239.
- Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 15:389-443.
- Peters M, Oeltze S, Seminowicz D, Steinmetz H, Koenke S, Jancke L (2002) Division of the corpus callosum into subregions. *Brain Cogn* 50:62-72.
- Sadato N, Ibanez V, Deiber MP, Hallett M (2000) Gender difference in premotor activity during active tactile discrimination. *Neuroimage* 11:532-540.
- Saron CD, Foxe JJ, Simpson GV, Vaughan HG Jr (2003) Interhemispheric visuomotor activation: Spatiotemporal electrophysiology related to reaction time. In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 171-219. Cambridge, MA: MIT Press.
- Semmes J (1968) Hemispheric specialisation, a possible clue to mechanism. *Neuropsychologia* 6:11-26.
- Soroker N, Kasher A, Giora R, Batori G, Corn C, Gil M, Zaidel E (2005) Processing of basic speech acts following localized brain damage: a new light on the neuroanatomy of language. *Brain Cogn* 57:214-217.
- Thompson PM, Schwartz C, Lin RT, Khan AA, Toga AW (1996a) Three-dimensional statistical analysis of sulcal variability in the human brain. *J Neurosci* 16:4261-4274.
- Thompson PM, Schwartz C, Toga AW (1996b) High-resolution random mesh algorithms for creating a probabilistic 3D surface atlas of the human brain. *Neuroimage* 3:19-34.
- Thompson PM, MacDonald D, Mega MS, Holmes CJ, Evans AC, Toga AW (1997) Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. *J Comput Assist Tomogr* 21:567-581.
- Tompkins CA (1995) Right hemisphere communication disorders: theory and management. San Diego, CA: Singular Press.
- Witelson SF (1989) Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain* 112:799-835.
- Witelson SF, Goldsmith CH (1991) The relationship of hand preference to anatomy of the corpus callosum in men. *Brain Res* 545:175-182.
- Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC (1998) Automated image registration: II. Intersubject validation of linear and nonlinear models. *J Comput Assist Tomogr* 22:153-165.
- Zaidel E, Iacoboni M (2003a) *The parallel brain*. Cambridge, MA: MIT Press.
- Zaidel E, Iacoboni M (2003b) Poffenberger's simple reaction time paradigm for measuring interhemispheric transfer time. In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 1-8. Cambridge, MA: MIT Press.
- Zaidel E, Iacoboni M (2003c) Does the CUD in SRT measure IHTT? Or: Is the crossed-uncrossed difference in the simple reaction time task a pure measure of interhemispheric transfer time? In: *The parallel brain* (Zaidel E, Iacoboni M, eds), pp. 259-266. Cambridge, MA: MIT Press.
- Zaidel E, Aboitiz F, Clarke J (1995) Sexual dimorphism in interhemispheric relations: anatomical-behavioral convergence. *Biol. Res.* 28:27-43.
- Zaidel E, Kasher A, Soroker N, Batori G, Giora R, Graves D (2000) Hemispheric contributions to pragmatics. *Brain Cogn* 43:438-443.